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PHYSIOLOGICAL CHEMISTRY.—*Chemical structure and physiological action.*[1] C. L. ALSBERG, Bureau of Chemistry.

The subject matter which I propose to present to you tonight contains nothing essentially new to the pharmacologist. It deals, however, with a field of research that, while of the greatest importance to the welfare of mankind, is still very much in flux. However, a subject in flux is more interesting than one that is in a static state with all phenomena accurately ticketed and labeled. It still permits the exercise of the imagination. Hence what I have to offer to you tonight must be, in the main, a series of speculations and of observations none too well coordinated. Only a part of it has found its way into the general text-books, and this is my excuse for the selection of my subject.[2]

Paracelsus wrote many centuries ago, "The real object of chemistry is not to make gold, but to prepare medicine." Schmiedeberg has defined the aim of the science of pharmacology as the production of physiological reactions with chemical reagents. The pharmacologist hopes, therefore, to contribute toward the solution of some of the problems of biology by using chemical stimuli as the physiologist uses physical ones. Some pharmacologists have believed that the reaction of living things to chemical stimuli is necessarily the result of a chemical reaction between the stimulating chemical and some substance in the cell stimulated. The hope has been expressed that eventually it will be possible to write the equations for these reactions as for any other chemical reaction. However, this hope is very very far from realization, and perhaps never will be realized because, as we shall see, it represents far too simple a conception of the matter. Indeed, almost the only case that occurs to me in which it is possible

[1] Address of the retiring President of the Washington Academy of Sciences. Presented at a joint meeting of the Academy and the Chemical Society on January 20, 1921. Received July 20, 1921.

[2] L. SPIEGEL. *Chemical constitution and physiological action.* Translated, with additions, from the German, by C. LUEDEKING and A. C. BOYLSTON (D. Van Nostrand Co., New York, 1915).

to write such a reaction is carbon monoxide poisoning. In this intoxication the carbon monoxide gas unites in fixed proportions with the hemoglobin of the blood to form a very stable combination which is incapable of transporting oxygen from the lungs to the tissues. The result is asphyxiation, but even in this case we are not helped much by our ability to write this equation, for it tells us nothing about the processes that take place during asphyxia. Indeed, we know very little about them. Carbon monoxide is the cause of death. The more immediate cause, however, is oxygen starvation, and if we are very exacting, we must demand the equations of asphyxia. These, however, we are quite unable to give.

Of recent years very different conceptions have been developed. The older men, dominated by the imagery of organic chemistry, sought the chemical reactions underlying the phenomena of pharmacological action, thinking that they are ordinary stoichiometric reactions, very complex ones if you will, but still of the ordinary type and, therefore, dependent upon the chemical properties of the substances taking part in them. In those days the prevailing conception of protoplasm was that it consisted of huge, very complex, very unstable molecules. The various parts of such a live molecule were believed to have different functions. According to this conception, the live molecule might have been pictured as resembling a chestnut burr bristling with prickles or grappling hooks each capable of grappling a specific and different food substance.[3] Some of the poisons were supposed to be anchored by such grappling hooks just like foodstuffs and the specific action of a given substance upon a given cell or tissue was supposed to be due to the fact that that substance had some inherent property that caused it to be anchored by some specific grappling hook in that cell. Therefore, explanation of the physiological action of a substance was sought primarily in the structure of its molecules rather than in its physical properties. To some particular grouping of the atoms in the molecule solely was attributed the physiological action of the substance.[4] Such a group was spoken of as the carrier of the action, and much was written about "toxophore" groups,

[3] P. EHRLICH. *On immunity with special reference to cell life.* Croonian Lecture. Proc. Roy. Soc. London **66**: 432–437, 446.

[4] O. LOEW. *Ein natürliches System der Giftwirkungen.* (Stuttgart, 1893.) P. EHRLICH. *Ueber die Beziehungen von chemischer Constitution und pharmakologischer Wirkung.* Vortrag gehalten im Verein fur Innere Medicin am 12 December, 1898. v. Leyden Festschrift p. 647. (August Hirschwald, Berlin, 1902.)

"anaesthetic" groups, "narcotic" groups, "tetanic" groups, and the like.

Our present-day conception of protoplasm is different. We no longer think of a giant living molecule so unstable that its decomposition and continuous reconstruction constitute the phenomena of life. We no longer consider protoplasm as homogeneous. We believe it to be heterogeneous, to consist of a series of phases, an emulsion, a series of fine droplets and particles in suspension.[5] According to the laws of surfaces, which I shall have to ask you to take for granted tonight, as we have no time to consider them now, some substances will concentrate at surfaces and this concentration will be greater the greater the curvature of the surface.[6] Therefore, in such a system as an emulsion you have membranes formed automatically at all surfaces, and so it seems to be with protoplasm. You must conceive of these as chemical membranes, as mere surface layers, not necessarily visible under the microscope, representing the very great concentration at the surface of a droplet of one or more of the substances dissolved in the droplet or in the surrounding medium. Each droplet is then a sort of test tube shut off to a certain degree from the other droplets and from the liquid in which it is suspended. Phenomena can therefore go on in such a droplet without affecting the other droplets except indirectly. Such a conception of protoplasm very greatly simplifies, as we shall see later, our conception of the physiological action of chemical substances since instead of being a purely chemical concept it is physical as well as chemical. It leaves room for such considerations as the surface effect of the substance, its solubility in the membrane, in the droplet, in the various phases of a gel, etc., etc.

With the old conception of protoplasm as a homogeneous chemical entity the physiological action of a substance was referred merely to its chemical character and reactivity. This point of view impeded rather than aided progress. With the acceptance of the idea of protoplasm as a physical system, rather than as a chemical structure, the conviction has gained ground that the physiological action of a substance depends not merely upon its chemical structure but also upon its physical properties, or rather those properties[7] that lie on the frontier between physics and chemistry, such properties as solubility, diffusi-

[5] C. L. ALSBERG. *Mechanisms of cell activity.* Science N. S. **34**: 97–105. July 28, 1911.

[6] W. M. BAYLISS. *An introduction to general physiology.* (Longmans, Green & Co., London, 1919.) Chap. I.

[7] G. GIEMSA. *Neuere Ergebnisse der Chemotherapie.* Archiv Pharm. **257**: 194. 1919.

bility, dissociation, colloidal state, electrical charge and the like. Of course, in the last analysis the physical state is but an expression of the chemical constitution and vice versa, but these are problems for the chemist, not the pharmacologist.

However, I do not mean to be understood as stating that chemical constitution has nothing to do with physiological action. I mean merely that very frequently changes in constitution produce changes in action chiefly because they influence the physical properties of the substance rather than its power of reacting chemically with other substances. Certainly very slight changes in constitution often produce very great changes in physiological action. You all know that stereo-isomerism influences the taste of simple amino acids, some being sweet, some bitter;[8] that one form of asparagin is sweet while the enantiomorphous form is tasteless; that l-adrenalin causes the smaller arteries to contract greatly while d-adrenalin is far less active.[9] The examples might be multiplied almost indefinitely. Indeed, as we shall see later, substances of a very widely different chemical structure may have a very similar action. Of these we may be sure that their action depends rather upon their physical than their chemical properties.

What I have to say tonight will deal as much with physical or physico-chemical properties as with chemical constitution. Moreover, I do not propose to deal with many simple inorganic substances like arsenic, iodine or phosphorus. The physiological action of many of the elements seems to be an intrinsic property as much as their atomic weight. Indeed, within the same group of the periodic system the toxicity of kations, with certain exceptions, increases with the increase of the atomic weight.[10] Until we know far more than we do now concerning the underlying causes for the physical properties of the elements we are not likely to know why, for example, iron is less poisonous than cobalt. It is much the same question as why bromine is red and chlorine green. We do know, however, that elements like arsenic, phosphorus and nitrogen, which exhibit variable valence, may be toxic and we suspect that their action is probably in some way connected with their change from one state of valence to another. We also know that in some way the toxic action of kations and anions is

[8] E. OERTLY and R. G. MYERS. *A new theory relating constitution to taste.* Journ. Amer. Chem. Soc. **41**: 861. 1919.

[9] W. H. SCHULTZ. *Quantitative pharmacological studies: Adrenalin and adrenalin-like bodies.* Hygienic Lab. Bull. **55,** U. S. Public Health and Marine Hospital Service, 1909.

[10] BLAKE. Compt. rend. 1839; Proc. Roy. Soc. London 1841. Amer. Journ. Sci. 1874; Ber. deutsch. Chem. Ges. **14**: 394. 1881.

related to their effects upon colloids, especially proteins;[11] but here again the power of kations to precipitate proteins and of anions to produce the reverse effect is, so far as our knowledge at present goes, an intrinsic property. Since it is, speculation upon these phenomena is rather fruitless till the physicists have gone a great deal further. I shall deal tonight therefore in the main with substances more complex than the simple elements.

There are in the main three general ways in which a substance may affect a cell:

The substance may attack the surface of the cell.

The substance may affect the cell indirectly without entering it.

The substance may affect the cell in the course of entering, or after entrance into the cell.

Many substances destroy the surface layer of a cell by precipitating or coagulating it. This is the effect of many astringents, such as the salts of many heavy metals, ferric chloride for example, when in sufficient concentration. Other substances dissolve some of the constituents of the surface layer as, for example, ether when in sufficient concentration.[12] Other substances combine with some component of the surface layer. This may be the action of saponins.[13]

Substances which neither enter cells nor attack the cell surface act chiefly by affecting the concentrations within the cell. They either withdraw water from the cell so that it tends to shrivel and become desiccated, or they cause water to penetrate into the cell so that it swells. These processes are called plasmolysis because they may, if carried to extremes, cause the protoplasm to disintegrate. Those among you who are botanists or physiologists know that this phenomenon may be studied by observing the behavior of suitable plant cells or red blood corpuscles when placed in solutions of the substances to be tested. In many plant tissues the protoplasm forms a layer lining a rigid cellulose wall. It is really a sac enclosing a relatively large space filled with sap. When such a cell shrinks or is plasmolyzed the protoplasm withdraws from the cellulosic cell wall and this can be seen very easily under the microscope. In the case of red blood corpuscles, these become crenated, that is, they shrink and take on the

[11] BAYLISS, op. cit., p. 35.

[12] L. HERMANN. *Ueber die Wirkungsweise einer Gruppe von Giften.* Arch. Anat. Physiol. u. Wiss. Med. **1866**: 27.

[13] H. E. WOODWARD and C. L. ALSBERG. *A comparison of the effect of certain saponins on the surface tension of water with their hemolytic power.* Journ. Pharm. Exp. Therap. **16**: 237. 1920.

appearance of a globe studded with projections like the head of a crusader's mace.

That a substance may plasmolyze a cell it is obvious that it must fulfill certain conditions. It must exert osmotic pressure; it must not be able to penetrate into the cell, or if it does, it must do so very slowly, that is, more slowly than water, for if it passes quickly into the cell the osmotic pressure within and without will be very quickly equalized and there will be no plasmolysis. In other words, the cell-membrane must be semi-permeable to the plasmolyzing substance. A semi-permeable membrane is one that permits only certain dissolved substances to pass through it. Now most cell-membranes are semi-permeable to most salts of organic as well as inorganic bases, to the sugars and to many other substances. They do not permit these substances to pass through readily. When brought into solutions of such substances, cells may be plasmolyzed. One group of organisms seems to form an exception. A large number of bacteria do not seem to be surrounded with membranes semi-permeable in this sense; salts pass into them apparently unhindered. They all can be stained according to the method of Gram, and are known as the Gram positive bacteria. They cannot be plasmolyzed.

Considerations of this sort help us to understand the action of certain salts and other substances upon the intestines. You all know that Glauber's salt (sodium sulfate) and Epsom salt (magnesium sulfate) are laxatives. Now one of the characteristics that distinguish such salts from others, say sodium chloride, is that they are not readily absorbed through the intestinal wall. Not being absorbed readily they cause the osmotic pressure of the intestinal contents to remain great as the food passes down the alimentary canal. In order to withdraw water from the intestinal contents the intestines would have to do an amount of osmotic work which would be very great indeed. The result is that water remains in the intestinal contents or is secreted into it so that the contents remain bulky and peristalsis is stimulated. This is one of the main factors, though not the only factor, in the purgative action of these salts. It is a physical factor dependent upon the slow absorption of these salts through colloid membranes, rather than upon any strictly chemical reaction dependent upon the structure of the molecule or its chemical reactivity.

We have seen that the phenomenon of plasmolysis furnishes a method to tell what substances do not enter cells. Conversely we can tell what substances do pass readily into cells, for such substances will not

plasmolyze. A study of the plasmolyzing power of many hundreds of substances has shown that substances of the most diverse chemical character can enter cells readily. They have neither molecules of similar size, nor similar melting points nor similar boiling points, nor similar chemical affinities. They have one property in common; they are more freely soluble in fatty oils and lipoids than in water. If any of these substances be mixed with water and oil, much of the substance will dissolve in the oil and relatively little in the water. As the physicist would put it, the distribution coefficient for these substances between oil and water is greatly in favor of oil.[14]

A very good illustration of this phenomenon is furnished by glycerin and its derivatives, mono- and dichlorhydrin.[15] Glycerin enters cells very slowly, monochlorhydrin quite rapidly and dichlorhydrin almost instantaneously. Glycerin has no narcotic action, monochlorhydrin has a fairly strong narcotic action and dichlorhydrin quite a powerful narcotic action. In the days of the purely chemical conception of protoplasm, it would have been assumed that chlorine was a "toxophore" group,[16] that perhaps its action depended upon its electronegative character or that mono- and dichlorhydrin had greater affinity for the cell-substance. The fact is that glycerin is but slightly soluble in oil and very soluble in water while its chlorine derivatives are very much more soluble in oils than in water.[17]

Since so many substances that pass readily through the semi-permeable cell membranes are oil-soluble, many biologists have concluded that the cell membrane is, in part at any rate, composed of fat-like substances, probably lipoids, like lecithin and cholesterin. This inference is based on the fact that it has been shown for a great variety of semi-permeable membranes that they permit only those substances to pass through them that are soluble in them. Thus chloroform, but not alcohol, may be made to pass through rubber membranes. Hence it was inferred that since only fat-soluble substances pass readily through the semi-permeable membranes of cells, these membranes must consist, in part at any rate, of fats or fat-like substances such as

[14] E. OVERTON. *Studien ueber die Narkose.* (Jena, 1901.) H. MEYER. Arch. exp. Path. Pharm. **42:** 109. 1899; **46:** 338. 1901. P. EHRLICH. Therap. Monatsh., March, 1887.

[15] E. OVERTON. *Ueber die allgemeine osmotische Eigenschaften der Zelle.* Vierteljahrb. Naturforscherges. Zurich **44:** 889. 1899.

[16] C. R. MARSHALL and H. L. HEATH. *The pharmacology of the chlorhydrins, a contribution to the study of the relations between chemical constitution and pharmacological action.* Journ. Physiol. **22:** 1, 2. 1897.

[17] H. KIONKA. *Zur Theorie der Narkose.* Arch. Int. Pharmacodynamie et Therapie **7.**

the lipoids and cholesterin. This is the more probable as lecithin and cholesterin have but slight surface tension effect and would therefore tend to accumulate at surfaces.[18] Indeed it is probable that all substances that lower surface tension must tend to accumulate at surfaces and take part, to a greater or lesser degree, in the formation of such membranes whether such substances come from within the cell or from the liquids that bathe the cell.

This hypothesis of the semi-permeability and lipoid character of the cell-membrane has not been accepted universally. Czapek,[19] for example, believes that the ability of substances to pass through the cell-membrane is a function of their ability to affect surface tension rather than a function of their oil solubility. However, substances that lower surface tension seem also to be oil-soluble. Perhaps the two traits are but expressions of the same underlying physical property. Shryver[20] believes the semi-permeability to be dependent upon the presence of a gel in the membrane. However, all the theories explaining the semi-permeability of cell-membranes that have been advanced of recent years are based upon physical or physico-chemical considerations. Not one assumes any dependence upon molecular structure or chemical reaction. That is the important point for us this evening.

We see then that the factors that determine the power of substances to enter cells are physical properties rather than molecular structure or chemical reactivity. If we examine the action substances exhibit after they have obtained entrance into cells, we find that an immense number of substances cause narcosis. In the lower organisms protoplasmic streaming and other forms of motion cease. In the higher organisms endowed with a nervous system, this undergoes a more or less complete paralysis. The most diverse substances have this effect:—Pentane, chloroform, ether, alcohol, phenanthrene, salicylamid monacetin. They have no common chemical properties except that they are neither acids nor bases. They are spoken of as the "indifferent narcotics" to distinguish them from the narcotic alkaloids which are bases. We have here again a common physiological action de-

[18] It should, however, be noted that many food substances, for example glucose, cause plasmolysis; yet they must enter cells for otherwise they could not nourish them. There are undoubtedly other factors that enter into the structure of cell-membranes and a number of theories on the subject have been advanced.

[19] F. CZAPEK. *Ueber die Oberflächen-spannung und den Lipoidgehalt der Plasmahaut in den lebenden Pflanzenzellen.* Ber. deutsch. botan. Ges. **28:** 480. 1910.

[20] S. B. SHRYVER. *Investigations dealing with the phenomena of "clot" formations, Part II.* Proc. Roy. Soc. B **87:** 366. 1914.

pendent apparently upon a common physical property exhibited by substances of the most diverse chemical structure.[21]

That this relation is not accidental is proven by the fact that the narcotic power of these substances is broadly proportional to their relative solubility in oil as compared with their solubility in water; that is, proportional to their distribution coefficient between these two solvents. The more this ratio is in favor of oil the more narcotic the substance. This was proved for a large number of substances, both by H. Meyer[22] and by Overton[23] who experimented with tadpoles. These animals were placed in water containing varying concentrations of the substance to be tested and the effect noted. In this way the lowest concentration capable of narcotizing the tadpoles was determined. Comparison of the minimum narcotic concentration thus determined for a large number of substances demonstrated that these concentrations show a direct parallelism with the distribution coefficients of the respective narcotics between oil and water.

This parallelism of the effective narcotic strength of a substance with its oil-water distribution coefficient is demonstrated strikingly if experiments be made, as was done by Meyer[24] with the same substances at different temperatures. The narcotic power of each substance changes with the temperature in proportion to the shift made by the temperature in the oil-water distribution coefficient. This is especially striking in the case of chloral as will appear from an examination of table 1 which has been adapted from Meyer's publication on this subject.

It is obvious that experiments analogous to Overton's tadpole experiments can be performed upon animals breathing through lungs instead of gills only with volatile narcotics like ether or chloroform. The non-volatile narcotics cannot be tested in any direct way because when given by the mouth the rate of absorption from the alimentary tract may vary in different individuals and in the same individual at different times. Moreover the rate varies with the solubility of the narcotic in the contents of the intestinal tract. Thus phenanthrene is not sufficiently soluble in water to be absorbed and exert any action though it has actually narcotic power. Long ago Bert showed that

[21] L. HERMANN, op. cit.

[22] H. MEYER, op. cit.

[23] E. OVERTON, op. cit.

[24] H. MEYER, *Zur Theorie der Alkohol Narkose.* III Mittheilung. *Der Einfluss wechselnder Temperatur auf Wirkungstärke und Theilungs-Coefficient der Narcotica.* Arch. exp. Path. u. Pharmakol. **46**: 338. 1901.

narcosis through the inhalation of air containing vapors of narcotics did not take place however long such a mixture was breathed unless the vapor pressure of the narcotic was above a definite threshold value.[25] The narcosis-producing vapor pressures run parallel in a general way with the oil-water distribution coefficients of the different

TABLE 1.—THE RELATION OF THE POWER OF CERTAIN SUBSTANCES TO NARCOTIZE TADPOLES AT DIFFERENT TEMPERATURES, TO THE DISTRIBUTION COEFFICIENTS OF THESE SUBSTANCES BETWEEN WATER AND OIL AT THESE TEMPERATURES

| Distribution coefficient | Threshold narcotic value in normal solution | Substance |
|---|---|---|
| 0.026 | 1/3 | Alcohol at 3° C. |
| 0.047 | 1/7 | Alcohol at 36° C. |
| 0.053 | 1/50 | Chloral at 3° C. |
| 0.066 | 1/70 | Monacetin at 36° C. |
| 0.093 | 1/90 | Monacetin at 3° C. |
| 0.236 | 1/250 | Chloral at 30° C. |
| 0.437 | 1/200 | Benzamid at 36° C. |
| 0.672 | 1/500 | Benzamid at 3° C. |
| 14.000 | 1/600 | Salicylamid at 36° C. |
| 22.230 | 1/1300 | Salicylamid at 30° C. |

volatile narcotics.[26] It is moreover curious to note that the effective vapor tension of the narcotic in the blood of the narcotized animal is of the same general order of magnitude, if calculated for the same body temperature, in the animal series from the frog to the dog.[27]

Meyer and Overton assumed that since the narcotics are especially soluble in the lipoids they will, of necessity, accumulate in those parts of the body that are richest in lipoids. The nervous system is peculiarly rich in lipoids. Hence these investigators explained in this manner the accumulation of the lipoids in the nervous system and their selective action upon it.[28] However, just as the lipoid theory of semi-per-

[25] P. BERT. *Sur la mort par l'action des mélanges d'air et de vapeurs de chloroform.* Compt. rend. Soc. Biol. **35**: 241. 1883.

*Méthode d'anaesthésie par les mélanges doses d'air et de vapeurs de chloroform.* Ibid. 409. *Sur l'anaesthesie par l'ether.* Ibid. 522.

[26] E. OVERTON, op. cit. p. 85.

[27] H. WINTERSTEIN. *Die Narkose* (Julius Springer, Berlin, 1919), p. 33.

[28] Meyer and also Overton believed that the indifferent narcotics accumulated most in the cortex because, according to the older analyses of the brain, the cortex is richest in lipoids. Bethe, however, pointed out that, according to more recent analyses of Thudichum, Koch and others, the white matter is far richer in lipoids than the gray; and Bethe dwelt upon this as one of the objections to this hypothesis. However, there is no good reason to suppose that interruption of the association tracts is not capable of producing narcosis as readily as direct action on the cortical cells themselves.

meability has not been generally accepted, so the Overton-Meyer lipoid theory of narcosis is not accepted universally. Traube believes surface tension effect and not lipoid solubility is the main factor and others believe that adsorption of the narcotic by the nerve cell is the main factor.[29] This is not the place to discuss these hypotheses other than to point out that none of them considers the chemical structure of the narcotic molecule as of moment except in so far as the chemical structure of the molecule determines its physical properties.

We may therefore fairly assume that in the case of the indifferent narcotics we have an apparently specific action upon a specific organ, the nervous system, dependent quite as much upon the physical properties of the narcotic as upon its chemical structure. The older pharmacologists would have said that the narcotic acts upon the nervous system specifically because the nerve cell or the nerve cell protoplasm contains a specific chemical group which has a special affinity for the narcotic and combines or reacts with it.

Now these theories of narcosis explain why the nervous system attracts the narcotic, in other words, they give a simple physical explanation for the distribution of the narcotic within the body. They do not tell us in the least what the narcotic does after it accumulates in the cells. Concerning the nature of the action of the narcotic after it has accumulated within a cell a number of theories have been advanced. We have not yet enough experimental data to reach a decision and there is hardly time tonight for a full discussion of them. However it will be of interest to indicate the general character of some of them:—if protoplasm is essentially an emulsion or gel, one of the phases of which is oil-like, then the solution of the narcotic in the oil phase must greatly affect the character of this phase and its surface phenomena.[30] There will inevitably be a tendency to change the permeability of the membranes at the interfaces with a tendency to the redistribution of the protoplasmic components to conform to new conditions. The tendency must be to change the composition of the phases relatively. If the narcotic enters into adsorption combinations with components of the cell this too must alter the relative composition of the phases. If the adsorption be upon enzyme molecules the functioning of the cell would be disturbed correspondingly.[31] In either event, whether the narcotic dissolves in the oil

[29] H. WINTERSTEIN, op. cit.

[30] H. MEYER. *Zur Theorie der Alkohol-narkose.* I Mittheilung. Arch. exp. Path. u. Pharmakol. **42**: 112. 1899.

[31] H. WINTERSTEIN, op. cit. p. 276, ff.

phase or forms a blanketing adsorption layer about enzyme molecules, or does both, the effect must be to hasten certain normal processes and retard others. It is a well-established fact that many narcotics retard *extra corpore* many enzyme reactions, especially oxidations. It is also well established that in narcotized cells the oxidation metabolism, that is, respiration, is dampened. That the presence of narcotics also tends to hasten some protoplasmic processes is evident from the effect of such substances on the rate of autolysis, that is, the self-digestion of cells. Even small quantities of such substances as chloroform or toluol very rapidly hasten the onset of the autolysis of cells *in vitro*.[32] Apparently they hasten it because through lipoid solubility, surface tension effect, or adsorption, they disturb the balance of the protoplasmic phases with a resulting destruction of the coordinating mechanisms of protoplasm.[33] The intracellular enzymes then run riot and rapid autolysis results. Perhaps physical phenomena, similar in kind if not in degree, are involved in narcosis. Certainly in chloroform narcosis katabolism is increased. It is conceivable that in the manner above suggested a substance may exercise a profound effect upon a cell without necessarily entering into a chemical union with some constituent of the cell. That such a chemical union must of necessity precede the attack of a poison upon a cell was formerly very generally assumed.

In discussing phenomena of this character we must beware lest we generalize too widely. No one hypothesis is applicable to all cases. Thus there are cases in which it is perfectly well known that substances accumulate in cells because they combine chemically with some constituent of the cell. The alkaloids furnish an example. Tannic acid precipitates many alkaloids. Some algae contain tannic acid and when they are brought into solutions of the free alkaloids, the base,

[32] v. Schroeder long ago showed that the autolysis of yeast went on more rapidly in the presence of a little ether than without. Evidently ether does to yeast cells exactly what it does to red blood corpuscles; it lakes them, *i.e.*, it dissolves the lipoids of the cell-membranes making the latter permeable to intra-cellular substances, among them the enzymes. It seems that a process similar to hemolysis, called cytolysis, may occur in any cell. Probably this phenomenon underlies such pathological conditions as acute yellow atrophy of the liver which is characterized by an *ante-mortem* autolysis of the liver and perhaps other organs. It is quite conceivable that a toxic substance absorbed from the gut may lake or cytolize the liver cells destroying the coordination between their own ferments and setting these ferments free to work their own cells' destruction. It is significant that yellow phosphorus, chloroform and chloral hydrate, all lipoid-soluble substances, are capable, when taken by the mouth, of producing a pathological condition bearing considerable resemblance to acute yellow atrophy of the liver.

[33] C. L. ALSBERG. *Mechanisms of cell activity.* Op. cit.

which penetrates into the cells, is precipitated by the tannic acid. The formation of these precipitates may be observed under the microscope. The alkaloid being removed by precipitation, more alkaloid diffuses in until all the available tannic acid has been consumed. The alkaloid enters because the cell-membrane is permeable to it. Whether this permeability is due to lipoid solubility of the alkaloid, surface effect, or adsorption need not concern us now. Were there no tannin within the cell, only so much alkaloid would diffuse into it as is required to establish equilibrium between the interior of the cell and the medium bathing the cell. More, however, passes in because a part is combined firmly with the tannin. By such a chemical mechanism, as well as in the other ways above discussed, substances may accumulate in special organs or cells.[34]

The indifferent narcotics are substances that are not dissociated. The majority of the substances which readily permeate cells are not ionized. This is beautifully illustrated by the difference in the action of the free alkaloid bases and their salts, as shown by Overton. The former are more poisonous than the latter, at least to the individual cell. The free base alone is able to pass through the cell-membrane. In a solution of the base all of it is free to pass through the membrane. The solution of the salt only contains free base to the extent that the salt is dissociated. With a base as weak as the alkaloids united with the common very powerful acids, the amount of dissociation will be very slight. The action of the salt is therefore slower than that of the free base.

Analogous conditions seem to prevail in the case of inorganic salts. As a rule ions do not pass through cell-membrane and it is very doubtful whether the ordinary salts of the organism, most of which plasmolyze, enter cells as ions.[35] Certain inorganic salts, however,

[34] For other mechanisms, see W. SCHULEMANN, *Die vitale Färbung in ihrer Bedeutung für Anatomie, Physiologie, Pathologie und Pharmakologie.* Biochem. Zeitschr. **80**: 1. 1917.

[35] Apparently the fact that the lipoids, as shown by Thudichum, readily form colloidal solutions in water, has been overlooked by those who have speculated on the subject. Koch has shown that such solutions change the solubility of inorganic salts and render them soluble with the lipoid in ether. I myself have observed that if a solution of egg yolk in 10 per cent NaCl be extracted with ether a small amount of material giving the biuret reaction passes into the ether. A thorough study of the manner in which lipoids and proteins modify the solubility of such substances as glucose, amino-acids, and inorganic salts is needed. It may well be that it will furnish the key to the mechanism by which such food-stuffs enter cells. However, it should also be kept in mind that none of the hypotheses concerning the character of cell-membranes is capable of explaining completely the entrance into cells of all substances that undoubtedly get into them. I have been careful to

probably enter cells because they are more or less lipoid-soluble, for example, mercuric chloride, cadmium chloride and copper chloride. Perhaps for that reason they are so very toxic and antiseptic.

Perhaps the best summing up of the relative importance of chemical and physical factors in determining the action of toxic agents has been given by Barger and Dale in one of their papers upon the active principles of the ergot of rye: "but it by no means follows that the peculiar distribution of the action of nicotine or of the sympathomimetic amines depends on the existence of specific chemical receptors in the cells primarily sensitive to them, as supposed by Langley. Stimulation may be a chemical process but the fact that certain cells are preferentially stimulated by a certain group of substances such as our amines may mean that in those cells these substances readily reach the site of action; a supposition which is in accord with the view advanced by Straub."....."On the whole then the least unsatisfactory view in the present state of knowledge seems to us to be that which regards the existence of stimulant activities as dependent on the possession of some chemical property, the distribution, and, in the main, the intensity of the activity as due to a physical property."[36]

This thought will help us to understand the reasoning that is used in the production of synthetic drugs, that is, the science known as chemo-therapy. Chemo-therapy is the name given to that phase of pharmacology which deals with the production of drugs for special and specific purposes. Sometimes its aim is defined more narrowly as the search for chemical agents that will cure infectious diseases, that is, agents that will act as internal disinfectants for the diseased body. Since such substances are usually more or less poisonous for the body cells as well as for the parasite, much of chemo-therapeutic research aims to so modify the molecular structure of the toxic substance as to render it appreciably more toxic to the parasite than to the body cells of the host.[37]

We can then divide the aims of investigators in the field of chemotherapy into two groups; those that endeavor to influence the physical properties of drugs and therefore their intensity and place of action in the organisms, and those that endeavor to influence the chemical

attribute to the lipoid only a part of the observed phenomena. Schulemann, for example, attributes a large rôle to phagocytosis, a phenomenon undoubtedly largely dependent upon surface tension effects.

[36] Cf. also W. SCHULEMANN, op. cit.

[37] G. GIEMSA, op. cit. p. 190–191.

properties of drugs and their specific manner of action.[38]

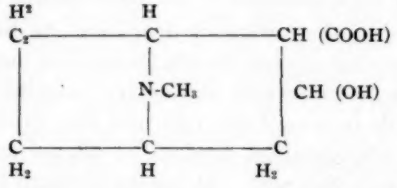
As no sharp line can be drawn between chemistry and physics so these aims of the synthetic chemist in the field of chemo-therapy can not be separated sharply. The attainment of one aim is very apt to bring the other in its train. Thus the rate of action of a drug may be accelerated or retarded by merely changing its solubility. The more soluble it is the more rapidly may it be absorbed and the more intense will be its action, since, obviously, the more rapidly it floods the body the more toxic will it be. At the same time its action is likely to be more evanescent because just as it will be more rapidly absorbed so it is apt to be more rapidly eliminated. The less soluble it is the more slowly will it be absorbed and the milder and more continuous is apt to be its action. Moreover, at the same time, changing its solubility may change the site of action of a drug as when it is rendered insoluble in the stomach but soluble in the intestines. Such an example is the tannate of an alkaloid. These tannates are insoluble in the stomach, but soluble in the intestines. Therefore not merely is their rate of action modified but the action itself may not begin until the drug reaches the intestines. The rate, the intensity, as well as the site of action have been modified by the mere change in solubility.

Similar changes in the action of drugs can be brought about by making derivatives that are inactive in themselves but are decomposed somewhere in the body setting the active principle free. By such means it is possible to retard the rate and also to change the site of action. Salol, a condensation product of phenol and salicylic acid, is a good example of this sort. It passes through the acid stomach but is esterified in the alkaline intestines with the gradual liberation of its component drugs. Thus they act slowly and less intensely, exerting local antiseptic action in the intestines and, after gradual absorption, continuous systemic action. A similar result is accomplished in the administration of inorganic substances if converted into un-ionized organic compounds. Such compounds may reach the tissues before they are decomposed, exerting their action at the site of decomposition. Salvarsan and its congeners are examples of this kind. They are organic compounds of arsenic which are but slowly decomposed within the tissues. By their use it is possible to keep the body continuously under the influence of arsenic without serious toxic symptoms. No doubt a part of the value of salvarsan is due to the

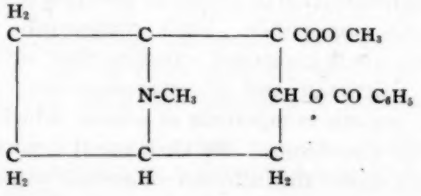
[38] S. FRAENKEL. *Die Arzneimittelsynthese auf Grundlage der Beziehungen zwischen chemischen Aufbau und Wirkung.* (J. Springer, Berlin, 1912.)

fact that it is retained in the system a long time and but slowly decomposed. In a very similar manner it is possible to make an element's action milder, more continuous and free from local irritant action. Iodoform is a case in point. Its action is that of iodine; but iodine itself is too powerful for local application to wound surfaces. Iodoform is slowly decomposed on wound surfaces subjecting them to the mild continuous action of iodine so that there is little local irritation.

Except for salvarsan, the cases just given are examples in which the modification of the action of the drug was in the main designed to accomplish a modification of the intensity and site of action of a well-known drug substance rather than to modify its specific action or to create a new drug with a modified specific or even a totally new physiological action. The investigations and the line of reasoning which lead up to the production of the valuable local anesthetic, novocaine, are perhaps typical of the latter form of chemo-therapeutic research. The object of these investigations was to develop a drug with the local anaesthetic action of cocaine but devoid of its objectionable toxic effects. Ecgonine, the mother substance of cocaine, has the following formula:



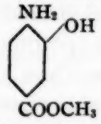

Einhorn[39] discovered that if he esterified the carboxyl (COOH) group of ecgonine with a methyl ($CH_3$) group and the hydroxyl (OH) group with a benzoyl group ($CO.C_6H_5$) he obtained the very anaesthetic natural base cocaine:



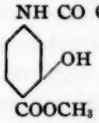

This led him to make a large number of benzoyl esters, many of which

[39] A. EINHORN. *Ueber neue Arzneimittel,* Ann. d. Chemie **371**: 125. 1909.

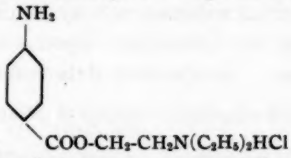
were anaesthetic. Indeed Filehne[40] concluded that the benzoyl group was responsible for the anaesthetic action. The action may be lacking if there are interfering groups such as the carboxyl (COOH) group of ecgonine. Moreover it was found that when, as in cocaine, the benzoyl group was combined with a nitrogen-containing nucleus its action became most apparent. Thereupon a large series of nitrogen-containing nuclei were benzoylated and it was found that so complex a nitrogenous nucleus as that of cocaine was not necessary. Many of these benzoyl esters derived from quite simple nitrogen-containing nuclei were found to have anaesthetic action. The first very simple substance of this type to find a practical use was orthoform, which is the methyl ester of para-amino-meta-oxybenzoic acid:




The objection to this compound is that it is too insoluble while its salts are too irritant. It was therefore necessary to make soluble derivatives. This was done by combining it with glycocoll (amino-acetic acid) derivatives. Thus there was produced a substance which has been used practically, nirvanin, the methyl ester of di-ethyl-amine-acetyl-para-amino-ortho-oxy-benzoic acid:




Further investigation showed that still greater simplification was possible by the elimination of the hydroxyl group. This led to the development of procaine, known by the trade name of novocaine, the soluble hydrochloride of para-amino benzoic acid di-ethyl-amino-ethyl ester or para-amino-benzoyl-di-ethyl-amino ethanol:




This is quite a simple substance as compared with cocaine and easily made synthetically. Another simplification is the removal of the

[40] W. FILEHNE. *Die local anaesthesirende Wirkung von Benzoylderivaten.* Berliner klin. Wochenschr. **24**: 107. Feb. 14, 1887.

amino ($NH_2$) group from the ring as in stovaine and alypine.

However, the power to anaesthetize the sensory nerve endings is not limited to basic substances like those above described. Many substances quite unrelated to them possess this power to a greater or less degree, such as antipyrine, certain inorganic salts, quinoline derivatives, phenolic and aromatic side-chain alcohols.[41] Some of the latter, like benzyl alcohol, phenethylol, benzoyl carbinol and saligenin, promise to compete with substances of the procaine type.

That so many substances of such varying molecular configuration exhibit similar physiological action arouses the suspicion that, as in the case of the indifferent narcotics, some as yet unrecognized common physical property is concerned in their action. Significant in this connection is the fact that Schleich modified the method of terminal anaesthesia by showing that if hypotonic solutions, that is, solutions of a lesser osmotic concentration than the blood, be injected under pressure until the tissues become rigid, the concentration of the anaesthetic necessary to prove effective is reduced. Now either hypotonic or hypertonic inorganic salt solutions tend to produce local anaesthesia by themselves, perhaps through merely causing swelling or shrinking of the cells, that is partial plasmolysis.[42] It is also significant as bearing on the possibility of some common physical property of the local anaesthetics that Gros[43] presents evidence that bases like cocaine and procaine are made more active if set free by sodium bicarbonate from their salts, presumably because they, like other alkaloids, enter cells most readily as the free base.[44]

The type of reasoning and experimentation which made a new era in surgery possible through the development of such substances as procaine is not limited to the production of new and valuable drugs. It has been applied with success to the production of new perfumes, of new antiseptics[45] and new flavoring materials.

As an example of the application of this manner of reasoning in the production of flavoring substances may be cited the work of E. K. Nelson in the Bureau of Chemistry upon capsaicin, the pungent principle of red pepper. Nelson first determined that capsaicin is a

[41] H. G. BARBOUR. *Local anaesthetics.* Science N. S. **51:** 497–504. May 21, 1920.

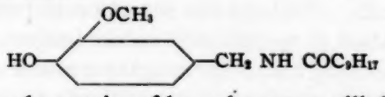
[42] BARBOUR, op. cit.

[43] O. GROS. *Ueber die Narkotika and Lokalanaesthetika.* Arch. exp. Path. u. Pharmakol. **63:** 80. 1910.

[44] Cf. supra, p. 333.

[45] *E. g.*, Dakin's Di-chloramin T.

vanillyl-decenoyl amide.[46]




He thereupon made a series of homologous vanillyl-acyl amides with acids of different molecular weights.[47] He found that with increasing molecular weight there was an increase in pungency up to a maximum beyond which it decreased. Table 2 gives the relative pungency of these substances, capsaicin being rated at one hundred.

TABLE 2.—COMPARATIVE PUNGENCIES OF VANILLYL-ACYL AMIDES

| | |
|---|---|
| Vanillyl n-hexoylamide | 5 |
| Vanillyl n-heptoylamide | 25 |
| Vanillyl n-octoylamide | 75 |
| Vanillyl n-nonoylamide | 100 |
| Vanillyl n-decoylamide | 50 |
| Vanillyl n-undecoylamide | 25 |
| Vanillyl n-dodecoylamide | 25 |
| Vanillyl undecenoylamide | 25 |

This phenomenon of increasing intensity of physiological action up to a maximum with increase in molecular weight and a diminution beyond the maximum with still further increase in molecular weight is a phenomenon that has been observed frequently.[48] There is good reason to believe that it is due, in part at any rate, to changes in solubility. For example, for a substance to be odorous it must be sufficiently soluble in both water and lipoids, since the cells of the mucous membrane of the nose are covered by a watery fluid and have in all probability a lipoid semi-permeable cell membrane.[49] Thus in the homologous series of pungent substances of table 2 the solubility in water decreases with rising molecular weight while the solubility in ether increases. Perhaps this is a plain case in which the manner of action, that is, pungency, is a function of the chemical structure of the molecule, while the intensity of action is dependent upon the physical property of solubility. Perhaps the specificity of the pungent action is not to be sought in the substances so much as in the taste buds of the tongue, according to the well-known physiological law of the specific response of the nerve end-organs. Any stimulus gives the

[46] E. K. NELSON. *The constitution of capsaicin, the pungent principle of capsicum.* Journ. Amer. Chem. Soc. **41:** 1115. 1919.

[47] E. K. NELSON. *Vanillyl-acyl amides.* Journ. Amer. Chem. Soc. **41:** 2122. 1919.

[48] TH. H. DURRANS. *The relationship between odour and chemical constitution.* Perfumery and Essential Oil Record **10:** 107–132. London, May 21, 1919.

[49] BACKMANN. Journ. physiol. path. gen. **17:** 1.

sensation peculiar to that organ. The capsaicin series is highly irritating to all cells. Perhaps the sensation of pungency is only the effect of the irritation of specific cells on the tongue.

The type of reasoning and of investigation above discussed has been used only recently to produce new repellants for insects, to combat human parasites. Moore and Hirschfelder[50] have made such a study upon the body louse and have demonstrated that the impregnation of the garments with certain halogenated cresols will repel this parasite for considerable periods. It would seem that here is a wide field for work. Research similar to that of Moore and Hirschfelder should lead to the discovery of repellants for such pests as black-flies and mosquitoes, a boon not merely to those who frequent the swampy lands of our continent but also to those who live in malarial regions.

While Moore and Hirschfelder and a few others have made a beginning in this sort of research in relation to insects troublesome to man, but little work has been done to improve or devise better insecticides and fungicides useful in agriculture. The economic losses from insect and fungous ravages are enormous. Despite such losses we have been content with relatively few simple insecticides and fungicides. The organic insecticides in present use are largely natural plant substances such as the poisons of the hellebore and larkspur, pyrethrum, and nicotine from the tobacco plant. In addition, cyanides, long known to be poisonous, and mineral oil emulsions are also used. Recently the employment of certain war gases has been advocated. Of the inorganic insecticides, arsenates, known for centuries to be poisonous to higher animals, and lime and sulfur sprays represent obvious and readily available substances. The use of fluorides represents a rather distinct and valuable discovery. No really synthetic organic substance has come into use as an insecticide. It is evident that the range of our insecticide and fungicide armamentarium at the present time is very narrow. There is no reason why this range could not be extended vastly by the development of a sister science to chemo-therapy, a science for which I venture to propose the name chemo-phyto-therapy. The aim of chemo-phyto-therapy would be to protect plants from the attacks of microorganisms and insects just as the aim of chemo-therapy is to protect animals from such attacks. As chemo-therapy demands the working together of pharmacologists and chemists, so chemo-phyto-therapy would demand

[50] W. MOORE and A. D. HIRSCHFELDER. *An investigation of the louse problem.* Research Publ. Univ. Minnesota **8**: No. 4. July, 1919.

the working together of entomologists, of pathologists and of chemists. The entomologist indeed has a twofold task. Not merely must he test out the substances created by the chemist, but he must also create the science of the pharmacology of insects.

Some desultory work of this type has been done in the past. The Bureau of Entomology of the U. S. Department of Agriculture from time to time has tested out numerous substances, often by-products for which no other use was apparent, such substances as naphthols, cresols, crude pyridin bases and many others. These were all found to be comparatively worthless for one cause or another. Few if any systematic studies in which the chemist and the entomologist cooperated seem to have been made. Such studies are now in progress through the cooperation of the Bureau of Entomology and of the Bureau of Chemistry. Notable progress has been made and it is hoped that a solid foundation will be laid for a new science—chemo-phyto-therapy.

My hope in addressing you was to give you a conception of the pharmacologist which is perhaps not generally current and to indicate to you how fundamental are some of the problems with which he deals. If I have succeeded in arousing your interest in this science and if in so doing I have demonstrated to you that the action of chemical substances upon living things is quite as much a function of the physical properties of such substances as it is of their molecular structure, then I have achieved the goal that I set for myself this evening.

PETROLOGY.—*Petrography of a lamprophyre dike cutting a pyrite body in Boyd Smith Mine, Louisa County, Virginia.*[1] THOMAS L. WATSON, University of Virginia.

The important large lens-shaped bodies of pyrite in Louisa County, Virginia, so vigorously worked for many years, are inclosed in schists of probable Cambrian age. These pyrite bodies, as well as the more or less closely associated gold deposits, are genetically related to intrusions of plutonic igneous rocks which are exposed in large masses in fairly close proximity to the ore bodies. The ore-bearing schists are also intruded in places by dikes of both acidic and basic igneous rocks, the latest of which is diabase of Triassic age.

Although the area is one in which igneous rocks, in part younger than the ore bodies, are fairly common, and in which mining operations have been in progress for a long period of years, not until recently

[1] Received June 16, 1921.

has a single instance been known where the pyrite bodies were intruded by igneous rocks.

The object of this paper is (1) to place on record observations of the only known case of a pyrite body in one of the principal pyrite mines of Virginia that is cut by a dike of igneous rock, and (2) to give a petrographic description of the rock, since it is unlike the usual types of basic igneous rocks found in the Virginia Piedmont province, and for the added reason that the mine is closed and is no longer accessible.

## OCCURRENCE

The lamprophyre dike[2] described in this paper cuts the pyrite body in the Boyd Smith mine which is located about 2 miles north of Mineral, Louisa County, Virginia. The mine is one of a group of pyrite mines located near Mineral that have yielded large tonnages of ore. According to Mr. Neustaedter, the dike was encountered in mining pyrite near the north heading of the so-called "west vein" on the first level about 100 feet below the surface. The ore body at this level is about 8 feet wide, strikes approximately N. 25° E., and dips to the southeast about 60°. The dike does not exceed one foot in thickness, cuts the pyrite body in an east-west direction, and dips about 85° south. The same dike was also observed cutting the "east vein" of pyrite. There is no evidence of the dike on the surface.

## PETROGRAPHY

*Megascopic characters.*—The general appearance of the rock is that of a typical porphyritic basalt. It is massive and of dark blue-gray color, with small phenocrysts of biotite and nearly black pyroxene in roughly equal amount set in a dense aphanitic groundmass. Polished surfaces of the rock are uniformly darker (nearly black) in color, with groundmass and phenocrysts rather strongly contrasted.

The dark minerals, biotite and pyroxene, are the only ones recognized in the hand specimen. Biotite, in small glistening crystals up to 2 mm. in diameter, but usually less than 1 mm., is seemingly more abundant than pyroxene in the hand specimen, but not in the thin section. Pyroxene, nearly black in color, is developed in lath-like prismatic crystals up to 5 mm. long and 1½ mm. thick, and in

[2] Credit for the discovery of the dike belongs to Mr. A. Neustaedter, former mining engineer in charge, to whom the writer is indebted both for a statement of facts relating to its occurrence and for a hand specimen of the rock. The discovery of the dike in 1917 by Mr. Neustaedter was communicated to the writer and a hand specimen sent, but pressing duties prevented the earlier preparation of a statement of the interesting occurrence.

short prismatic nearly equant crystals up to 4 mm. in diameter. The density of the specimen analyzed is 3.065.

*Microscopic characters.*—In thin section the rock shows considerable alteration, especially the goundmass, which is composed chiefly of clay substance admixed with more or less chloritic and serpentinous material, derived probably from either feldspars or feldspathoids or both. Neither feldspar nor glass was observed in the thin section studied, although both may have been present originally. The groundmass of the composition indicated above was roughly estimated at 30 per cent.

Phenocrysts of biotite, augite, and altered olivine make up probably 60 per cent or more of the rock. Augite and much of the biotite are usually fresh, but olivine is completely altered. The ore minerals, titaniferous magnetite and apatite, the former predominating, make up chiefly the remaining 10 per cent of the rock. No evidence of the presence of sulfide minerals was indicated in either the hand specimen or the thin section.

Biotite is of the type usually characteristic of the lamprophyres. It exhibits intense pleochroism in shades of light and dark brown, and in part dark-colored resorption rims. Much of it is entirely fresh, but some has altered to a faintly pleochroic red substance without trace of cleavage. It usually contains some inclusions.

Pyroxene is the variety augite near diopside in composition. Most of it is colorless but some individuals show narrow faintly pleochroic borders indicating some admixture of the aegirite molecule. Faint violet shades indicating the presence of titanium are also noted. The average extinction angle varies from 35 to 40 degrees. The augite occurs in several generations and probably formed during the entire period of crystallization of the rock. It is developed in subhedral short nearly equant and in elongated prismatic (bladed) crystals, the latter being predominant and so closely resembling in outline lath-shaped plagioclase in diabase as to suggest diabasic texture. In extreme cases the augite prisms are more than six times longer than thick. A pronounced zonal structure is usually developed in the nearly equant crystals, and some show hour-glass structure. Some crystals show a green core that is faintly pleochroic and sharply defined from the outer colorless part of the individual; others have a pale green faintly pleochroic outer zone enveloping a colorless core. The microscope indicates augite low in iron and in part titaniferous. Cleavage is usually well developed in the nearly equant crystals and

to a less degree in the lath-like forms. Twinning is observed in one or two of the crystals.

Olivine, originally present in amount roughly estimated at 18 per cent, is completely altered to greenish yellow serpentine, but the outlines of the original mineral are usually well preserved.

## CHEMICAL COMPOSITION

The composition of the rock is shown in the chemical analysis given in table 1. It is regretted that fresher material was not available for analysis, for the high water content (5.21 per cent) indicates considerable alteration of the rock, a fact fully confirmed by microscopic study.

TABLE 1.—ANALYSIS AND NORM OF LAMPROPHYRE DIKE, LOUISA COUNTY, VIRGINIA.

S. D. GOOCH, ANALYST

| | | | |
|---|---|---|---|
| $SiO_2$ | 37.40 | or | 15.01 |
| $Al_2O_3$ | 18.60 | ab | 4.19 |
| $Fe_2O_3$ | 6.35 | an | 40.87 |
| FeO | 7.95 | di | 0.68 |
| MgO | 3.80 | hy | 11.67 |
| CaO | 11.57 | ol | 0.48 |
| $Na_2O$ | 0.50 | mt | 9.28 |
| $K_2O$ | 2.53 | il | 7.45 |
| $H_2O-$ | 1.89 | ap | 4.70 |
| $H_2O+$ | 3.32 | | |
| $TiO_2$ | 3.89 | Symbol: II(III).5.4.2. | |
| $P_2O_5$ | 2.04 | | |
| MnO | 0.23 | No name for II.5.4.2. in the "Quantitative System." | |
| | 100.07 | | |
| Sp. Gr. | 3.065 | | |

Because of the altered condition of the rock the norm and mode do not agree. There is no name yet for the position in the "Quantitative System" of classification in which the rock falls, or for the next one in salfemane, but it is so altered (over 5 per cent of water) that it seems not advisable to propose one. The high $K_2O$ is undoubtedly contained in the biotite; $TiO_2$ mostly in the titaniferous magnetite or ilmenite, but partly in the augite, and probably to some extent in the biotite; while the high $P_2O_5$ is derived from apatite, which is present in larger amount than is usual for the average rock of this type.

## AGE

The exact age of the dike is unknown. The ore body which it cuts is one of several of similar composition occurring in the same district in Cambrian schists. The pyrite bodies are genetically related to intrusions of granitoid rocks that may be later but not older

than Cambrian, and with which the dike may possibly be correlated as a late differentiate. The youngest known igneous rocks in the district are dikes of Triassic diabase to which the dike cutting the pyrite body bears no resemblance as it is the first of its kind to be described from the Virginia Piedmont province. It cannot be older than Cambrian and may be as late as Triassic. The rock is more closely allied in mineral composition and structure with the Triassic dikes of basic igneous rocks than with the igneous bodies of earlier age occurring in the area. For these reasons the writer regards the dike as being probably not older than Triassic.

## ABSTRACTS

Authors of scientific papers are requested to see that abstracts, preferably prepared and signed by themselves, are forwarded promptly to the editors. The abstracts should conform in length and general style to those appearing in this issue.

OPTICS.—*Dispersion in optical glasses: I.* FRED. E. WRIGHT. Journ. Opt. Soc. Amer. **4**: 148–159. 1920. (Geophysical Lab. Papers on Optical Glass, No. 27.)

If partial dispersions alone are considered and plotted one against the other, the result in each case for a series of optical glasses is a straight line. This fact, that in a series of optical glasses the partial dispersions are related by linear functions and that these functions are the same for all glasses, proves that, if a single partial dispersion is given, the entire dispersion-curve is fixed, irrespective of the type of glass. This means that within the limits to which this statement holds, namely, about one unit in the fourth decimal place, if any partial dispersion is given, all other dispersions follow automatically. Thus, a series of standard dispersion-curves can be set up independent of the absolute refractive index. This means that if for any substance two refractive indices be given, the dispersion-curve can be written down directly; that in case two substances of very different refractive indices are found to have the same actual dispersion for one part of the spectrum their dispersion-curves are identical to one or two units in the fourth decimal place throughout the visible spectrum. From these relations it is possible to build up dispersion formulas containing two, three, or more constants which represent the data in the visible spectrum with a high degree of exactness. Certain of these formulas are of such form that they are valid far into the infra-red and ultra-violet, but break down of necessity as an absorption band is approached. Certain of the dispersion formulas thus obtained are well adapted for computation purposes. F. E. W.

GEODESY.—*Elements of map projection with applications to map and chart construction.* CHARLES H. DEETZ and OSCAR S. ADAMS. U. S. Coast and Geodetic Survey Spec. Publ. **68** (Serial **146**). Pp. 163, figs. 74, pls. 8. 1921.

The aim of the authors is to present in simple form some of the ideas that lie at the foundation of the subject of map projections. Many people have rather hazy notions of what is meant by a map projection, to say nothing of the knowledge of the practical construction of such a projection.

The subject matter is divided into two parts which are intended to meet the needs of such readers. The first part treats the theoretical side in a way that is as simple as it can be made; the second part takes up the consideration of the practical construction of some of the most important projections, the intention of the authors being to give such detailed directions as are necessary to present the matter in a clear and simple manner.

The use of mathematical analysis in the first part is studiously avoided since the intention is merely to illustrate the way in which different kinds of projection may arise when we attempt to produce maps with specific properties. Both the first and second part are profusely illustrated with figures that serve to make clear the statements of the text.

The projections described in the second part belong mainly either to the conformal class or to the equal-area class. Several tables for projections are included, the most important being that of a Lambert-zenithal equal-area projection for the United States or for North America with center on the parallel of 40°, that of an Albers equal-area projection for the United States, and finally, the most important of all, that of a general Mercator projection. As a closing section of part two and of the whole treatise, some general consideration is given to world maps, that is, to maps that are intended to include as great an extent of territory as a hemisphere or in certain cases to represent the whole sphere. C. H. D. and O. S. A.

PETROLOGY.—*Italite: a new leucite rock.* HENRY S. WASHINGTON. Amer. Journ. Sci. **50:** 33–47. 1920. Atti. Accad. Lincei **29:** 424–435. 1920.

A detailed account of the new leucite rock first described in this JOURNAL **10:** 270–272. 1920.

ZOOLOGY.—*Report on the ophiurans collected by the Barbados-Antigua Expedition from the University of Iowa in 1918.* AUSTIN H. CLARK. Univ. Iowa Studies. Studies in Natural History, 9 (First Series No. 45), No. 5, 29–63. March 15, 1921.

A history of the study of the ophiurans of the Caribbean region is given, with a list of the more important papers; the Caribbean echinoderm fauna is discussed, and the peculiarities of the West Indian ophiuran fauna are analyzed and compared with those of the crinoid fauna of the same region; the discontinuous distribution of the echinoderms is discussed and explained as resulting from the extirpation of ancient types from the more favorable areas in the sea so that they now exist only in isolated localities representing the extreme limits of their original habitat; a complete list of the West Indian ophiurans is given; the occurrence of these animals at Barbados and at Antigua is described, and all previous records from these islands are given; the specimens secured by the expedition are described in detail. A. H. C.

ENTOMOLOGY.—*The ants of the Fiji Islands.* W. M. MANN. Bull. Mus. Comp. Zool. Harvard **64:** 401–499, figs. 1–38. No. 5, 1921.

This is a report of the ants collected by the writer while in Fiji as Sheldon Traveling Fellow of Harvard. The insects of Fiji are not well known; hitherto but 53 species of the order Hymenoptera had been recorded from the islands. The present paper lists 78 species of ants, including many new species and several new genera and subgenera. Certain genera of ants are well developed in Fiji, among them the genus *Camponotus*, which is represented by ten forms belonging to a subgenus (*Myrmegonia*) which is confined to

the islands. About 70 per cent of the species listed are supposedly endemic. This number of endemic forms is an unusually high percentage for an island fauna and indicates a very long isolation.

In a preliminary discussion of the zoogeographical position of the islands it is shown that the ant fauna is not related to that of any one region but consists chiefly of types that formerly were of wide distribution and thus supports the idea that Melanesia has served, as far as the land fauna is concerned, as a biological conservatory. Fiji is the eastern limit of this region and has been isolated longer that the islands further west. W. M. M.

ENTOMOLOGY.—*Diptera of the superfamily Tipuloidea found in the District of Columbia.* C. P. ALEXANDER and W. L. MCATEE. Proc. U. S. Nat. Mus. **58:** 385–435, pl. 26.

This paper forms another one of the series of insect papers which endeavors to make it possible for local workers to become acquainted with the fauna of the District of Columbia and vicinity. The insects belonging to the superfamily Tipuloidea were commonly called crane-flies, and this paper tabulates all the species known to occur locally, gives notes on the habits of the adults and larvae, and distribution and dates of flight of the various species. The introduction briefly summarizes the history of this science as far as pertains to this region and the paper is followed by a bibliography of titles. One plate illustrates the venation. 40 genera are included. Of the species listed 87 are described from material which was collected in this region, chiefly by the activities of the late C. R. Osten Sacken. S. A. ROHWER.

ENTOMOLOGY.—*A revision of the North American species of Ichneumon-flies belonging to the genus* Apanteles. C. F. W. MUESBECK. Proc. U. S. Nat. Mus. **58:** 483–576. 1921.

The Ichneumon-flies of the genus *Apanteles* are small, usually black, insects which in the larval stage are parasitic on the larvae of lepidopterous insects. The above-mentioned paper is a revision of the species of North America, including the West Indies. The revision is based largely upon the extensive collections of the National Museum and 164 species are recognized. The types of most of the species have been studied by the author and besides pointing out some synonymy he has described 36 new species. The descriptive part of the paper is preceded by a synoptic key and followed by an aphabetical list of hosts, and a species index. S. A. ROHWER.

## PROCEEDINGS OF THE ACADEMY AND AFFILIATED SOCIETIES

### PHILOSOPHICAL SOCIETY

#### 849TH MEETING

The 849th meeting of the Philosophical Society of Washington was held in the Assembly Hall of the Cosmos Club on March 26, 1921. It was called to order by President FARIS, with 65 persons present. The program was as follows:

O. S. ADAMS: *Authalic latitude, a cartographic expedient.* (Illustrated.)

It has been found by many scientific investigations of various kinds that the shape of the earth, as a whole, is very nearly that of an ellipsoid of revolution with the equatorial diameter about 26 miles longer than the polar diameter, the axis of rotation of the generating ellipse. It is evident that

some regular body of this kind must be adopted to form the surface of reference for geodetic investigations as well as for geographical purposes; any irregularities that may be found to exist are viewed as departures from this regular form and can be taken into consideration, as such, whenever necessary.

Since this spheroid is taken as the surface of reference, it becomes the problem of cartography to take it into account in all mapping projects. It is comparatively easy to determine projections of various kinds for the sphere; hence mapping can be simplified if we determine an intermediate projection of the spheroid conformally upon a sphere with radius equal to the equatorial radius of the earth. This is done by applying a correction to the geodetic latitude and results in what is called the isometric latitude. In considering equal-area mapping of the spheroid with this fact in mind, the idea arose that the spheroid could be projected equivalently upon a sphere of equal surface by computing a correction to the geodetic latitude, the longitude being left unchanged just as in the case of the conformal mapping. This sphere could then be mapped upon the plane by any desired equal-area projection, and the result would be an equal-area projection of the spheroid. This idea of an intermediate projection was then developed analytically and the resulting latitude has been christened *Authalic latitude*. The term "authalique" was used by Tissot as a general term for equal-area. Authalic latitude is therefore "equal-area" latitude.

The difference between the geodetic latitude has been developed in a Fourier series and tables computed for every half degree of latitude. These results are published in U. S. Coast and Geodetic Survey Special Publication No. 67, entitled *Latitude developments connected with geodesy and cartography*.

The paper was discussed by Messrs. C. A. BRIGGS, PAWLING, SOSMAN and WILLIAM BOWIE.

E. A. ECKHARDT and J. C. KARCHER: *A chronographic recorder of radio time signals*. (Presented by Mr. ECKHARDT, and illustrated with slides and a demonstration of the apparatus.)

The radio time signal recorder described in this paper was devised at the Bureau of Standards for the field use of the Coast and Geodetic Survey. By its use the Survey will be enabled to record simultaneously on a chronographic drum the time signals sent out by Annapolis on the breaks of the local chronometer without mutual interference. Radio signals originating at Lyons, France, may be recorded at the Bureau of Standards whenever that station is sending, the air line distance between sending and receiving stations being approximately 3800 miles. It is inferred, therefore, that the sensitivity of the apparatus is sufficient to record Annapolis time signals at any field station which the Coast and Geodetic Survey may occupy anywhere within the borders of the United States.

The apparatus is sufficiently rugged for field service, and a 50-foot, 6-wire flat-top antenna 40 feet above the ground is sufficient for all ordinary conditions.

The radio apparatus proper may be used with any kind of chronograph drum or tape recorder. Dot and dash signals are indicated by short and long excursions of the recording pen from the datum line. In an Annapolis time signal these excursions are $^1/_3$ of a second long, while the pen traces the datum line during $^2/_3$ of every second.

The receiver equipment includes a regenerative electron tube circuit in the plate circuit of which there is a telegraph relay. This regenerative circuit starts to oscillate when the grid potential is made to exceed a certain critical

value. The passing of the circuit from the non-oscillating to the oscillating state results in a rise in plate current sufficient to operate the telegraph relay. The operation of the relay results successively in a pen excursion and in the killing of the local oscillations. The circuit is thus restored to the receptive state and the pen to the datum line.

A very small change in grid potential is sufficient to start oscillations if the grid potential is initially adjusted to a value near to and just below the critical potential. This potential rise may be provided by a radio signal received on an antenna suitably related to the regenerative circuit.

The circuits are so located that during the reception of radio signals the breaks of a local break-circuit chronometer may be recorded simultaneously by means of the same pen. This obviates lags which would be encountered if independent pens were used.

## 850TH MEETING

The 850th meeting of the Philosophical Society was held in the Auditorium of the Cosmos Club on April 9, 1921. It was called to order by President Faris with 31 persons present.

The first paper, on *Mollier diagrams*, by E. F. MUELLER and C. H. MYERS, was presented by Mr. Myers and was illustrated.

In 1904 Mollier published an article[1] in which he described the properties of heat content and its uses in refrigeration problems. This article is illustrated with (1) a heat content-entropy diagram with rectangular coordinates for steam, (2) a heat content-entropy diagram with oblique coordinates for $CO_2$, and (3) a heat content-pressure diagram for $CO_2$.

In the present paper the properties and uses of heat content were discussed, and illustrations of six diagrams shown in which the ordinates were heat content and the abscissas were entropy (rectangular coordinates), entropy (oblique coordinates), volume, log volume, log pressure, and a scale of pressure corresponding to a uniform scale of saturation temperature, respectively.

The choice of coordinates is a matter determined by conditions. Where the whole range from saturated liquid to a considerable superheat in the vapor is required the heat content-entropy diagram is poor even with the oblique coordinates since it covers only a small portion of the paper and the lines cross at sharp angles. The use of volume as abscissa is very little if any improvement, although the use of log volume is much better. The diagrams in which a function of the pressure serves as abscissa are very readable, although the pressure corresponding to a uniform temperature scale is probably the best when the diagram does not extend above the critical.

Some function of the heat content might be used for the ordinate in order to magnify the scale in parts desired to be especially accurate. The use of uneven coordinates should cause very little trouble if sufficient lines are entered in the diagram so that linear interpolation may be used.

The second paper, on *The heating of substances by expansion*, was presented by Mr. L. H. ADAMS, and was illustrated.

The pressure to which a fluid is exposed may be released by three principal methods:

(1) Isentropic expansion, *i.e.*, at constant *entropy*.

(2) Isenergic or explosive expansion, *i.e.*, at constant *energy*.

[1] Zeitschr. Ver. Deutscher Ingenieure.

(3) Isenkaumic or extrusive expansion, *i.e.* at constant *enkaumy*,[2] or constant heat content.

These three methods were discussed and attention was called to the large heating effects when liquids are expanded according to (3). Thus, water by expansion through a porous plug from a little over 4000 atmospheres should heat itself from 20 deg. to 100 deg. C.

Although the ordinary thermodynamic equations are applicable only to fluids, at pressures far in excess of their ultimate strength solids fulfill to a sufficient extent the condition of equality of pressure in all directions, and therefore the equation for isenkaumic expansion may be applied to such phenomena as the extrusion of wires and other solids through small openings.

The paper was discussed by Messrs. WHITE, MUELLER, C. A. BRIGGS, and HUMPHREYS.

The third paper, on *Specific and latent heats of nickel and monel metal*, was presented by Dr. W. P. WHITE, and was illustrated.

The addition of heat makes all bodies hotter, but the amount of heat required to raise a body 1 degree is different for different bodies. This quantity is the specific heat. It has important relations with the nature of atoms and energy. The principal key to this relation was one of Einstein's earlier discoveries. The specific heat at high temperatures is also of practical importance in the treatment of metals, fire brick, and all materials which have to be heated or cooled. An important economy in portland cement manufacture was effected some years ago by a recovery of heat based on a knowledge of the specific heat of the cement at high temperatures.

The simplest way to determine specific heat is to give a sample of the material in question a known amount of heat by means of an electric heater, measuring the change in temperature produced. This method works best in a vacuum and at low temperatures where the heat losses are small. It is almost the only method used at the low temperatures of liquid air and liquid hydrogen. Its value at high temperatures is questionable, and it has been little used. The irregularity which is unavoidable in most electric furnaces and the very rapid rate of heat loss at such temperatures are both difficulties. It is possible that by improved technique this method might be used at high temperatures. If so, it would be a very interesting research.

A more successful method at high temperatures is to heat a body in a furnace and then drop it into a water calorimeter so that the most difficult measurement, the measurement of heat, is carried out at room temperatures with all the refinements of modern technique. The only thing to be done in the furnace is then the heating of a body to constant temperature, for which abundant time can be allowed. The greatest source of error is still in the furnace, but this can be diminished if the distribution of temperature within the furnace is carefully studied. If the material is a metal which will oxidize in air it must be protected. One very ingenious method had been the inclosing of the furnace in a high vacuum. A long tube, also evacuated, led down into the calorimeter so that the body was in a vacuum from beginning to end. In work at the Geophysical Laboratory, the metal specimens were sealed up bulbs of silica glass which held up to 1450° C., the melting point of nickel, although they were somewhat soft at that temperature. Ordinary glass would have run like molasses in April at this temperature. The heat that may be lost in dropping the body through the air is not so serious as might be supposed, but it cannot be neglected. This source of error was

[2] A proposed new term derived from the Greek *καυμα*, heat.

eliminated in the present work, by first dropping empty containers and subtracting the heat given out by the empty container. If the heat loss is the same in each drop the subtraction eliminates it. To keep it the same it has been found necessary not to allow the escape of steam, which is likely to be irregular. Hence, second, the calorimeter contained a steam dome into which the steam could rise without getting out. A quick drop has often been accomplished by melting a platinum wire from which the specimen was hanging. After considerable trial a mechanical arrangement for dropping has been developed which is more convenient and less expensive. It was necessary to find a suitable material and then a compact design not calling for great strength.

The only results for many metals at high temperatures were recently obtained by three German investigators, who used the vacuum-closed furnace already mentioned. The results obtained in the Geophysical Laboratory for the latent heat of nickel were about 30 per cent higher than theirs. It is believed that the Geophysical Laboratory method, though simpler and easier to carry out, was free from several sources of error caused or aggravated by the limitations of working in vacuum, and that the result obtained at the Geophysical Laboratory, 73 calories per gram for the latent heat of nickel, is accurate at least to 5 per cent.

The paper was discussed by Messrs. FOOTE, MUELLER, SOSMAN, and others.

H. H. KIMBALL, *Recording Secretary.*

## SCIENTIFIC NOTES AND NEWS

Observations have recently been made by a Coast and Geodetic Survey party on the *Explorer* to verify the magnetic disturbance reported in the vicinity of Sentinel Point, southeastern Alaska. The maximum disturbance was found to be just west of the Point, the ship's compass changing its direction 55 degrees within a very short distance. The disturbance extends entirely across Port Snettisham, at one place amounting to more than 20 degrees in midchannel.

The securing of sea-water densities and temperatures has been begun by the Coast and Geodetic Survey observers at Portland, Maine, and Boston, Massachusetts. It is the intention of the Survey to secure similar observations at all the principal tidal stations.

At the invitation of Mr. NORTHCOTT, owner of the Luray Caverns, Virginia, Dr. ALES HRDLICKA of the National Museum visited the caverns on June 27 for the purpose of examining and removing certain bones, enclosed in stalagmite, which were believed to be human. After considerable difficulties, the entire deposit containing the bones was taken out in pieces which showed the remains of most of the parts of a human skeleton; but no trace remained of the skull with the exception of a portion of the lower jaw. The specimens have been donated to the Museum for further study.

The headquarters of the Chemical Warfare Service in Washington have been moved from the temporary buildings at 1800 Virginia Avenue to the seventh wing of the Munitions Building.

The Fixed Nitrogen Research Laboratory, together with about a half million dollars from the original appropriation made for the investigation of nitrogen fixation, was transferred on June 30 from the jurisdiction of the War Department to the Department of Agriculture. The Laboratory is now an independent unit of the Department of Agriculture, under the direction of

Dr. RICHARD C. TOLMAN, who has the assistance of an advisory committee made up of a representative of the War Department and representatives of the agricultural bureaus which are directly interested in the fixation of nitrogen. It is expected that the present allotment will maintain the Laboratory about two years.

A farewell dinner to Dr. CARL L. ALSBERG, chief of the Bureau of Chemistry, U. S. Department of Agriculture, was given at the Cosmos Club on June 17 by the chiefs of bureaus of the Department. Dr. Alsberg left Washington in July to become director of the new Food Research Institute established by the Carnegie Corporation at Stanford University, California.

Mr. CHARLES H. BEHRE, Jr., of Illinois, has been appointed assistant geologist with the U. S. Geological Survey.

The following have been appointed geologic aids with the U. S. Geological Survey: Messrs. WILMOT H. BRADLEY, of Connecticut; PLATT C. BENEDICT, of Massachusetts; JAMES GILLULY, of Washington; HAROLD W. HOOTS, of Kansas; KENNETH K. LANDES, of Washington; and LLOYD W. FISHER, of Pennsylvania.

Mr. MILTON N. BRAMLETTE, of Wisconsin, has been appointed assistant geologist with the U. S. Geological Survey.

Dr. HARDEE CHAMBLISS, formerly research chemist with the General Chemical Company, and lieutenant colonel in charge of U. S. Nitrate Plant No. 1 during the War, has been appointed to take charge of the work of the department of chemistry at the Catholic University on account of the prolonged illness of Rev. Dr. JOHN J. GRIFFIN, who has been in charge of the department since 1895.

Mr. LLOYD C. FENSTERMACHER, of Pennsylvania, who was recently appointed assistant geologist with the U. S. Geological Survey, was killed on July 9 in an automobile accident while engaged in field work for the Survey near Wilder, Montana.

Mr. G. J. FINK, formerly with the Hooker Electrochemical Company of Niagara Falls, is now associated with Dr. M. E. HOLMES in the chemical department of the National Lime Association in Washington.

Mr. PAUL M. FRANK, of Allentown, Pennsylvania, has been appointed assistant curator in the Division of Mineral Technology of the National Museum.

Dr. MICHAEL E. GARDNER has been apointed chief of the bureau of preventable diseases and director of the bacteriological laboratory of the U. S. Public Health Service.

Mr. JOSEPH L. GILLSON of Illinois has been appointed assistant geologist with the U. S. Geological Survey.

Dr. F. H. KNOWLTON of the National Museum received the honorary degree of Doctor of Science from Middlebury College in June.

Mr. CHARLES E. MIRGUET, who has been associated with the National Museum for several years, has been appointed taxidermist to succeed the late Mr. WILLIAM PALMER.

The sections of Eastern and Western Areal Geology in the U. S. Geological Survey have been merged into one section under the direction of Mr. SIDNEY PAIGE.